Medical and Pediatric Oncology 26:414–416 (1996)

Rothmund-Thomson Syndrome and Osteosarcoma

Isabelle Cumin, MD, Jean-Yves Cohen, MD, Albert David, MD, Françoise Méchinaud, MD, Hervé Avet-Loiseau, MD, and Jean-Luc Harousseau, MD

The Rothmund-Thomson syndrome (RTS), also called *poikiloderma congenitale* is a rare autosomal recessive disease first described in 1868. This syndrome includes most frequently seen skin lesions (atrophy, telangiectases, pigmentation), cataracts and bone defects (dysostosis, dysplasia). Some authors describe an association with malignancy. We report three cases of Rothmund-Thomson syndrome associated with osteosarcoma. After cutaneous epithelioma, osteosarcoma is the most frequent malignancy. Thus, patients with RTS need a careful survey. The treatment did not differ from sporadic osteosarcoma. Chemosensitivity and toxicity are also not different.

Key words: Rothmund-Thomson syndrome, poikiloderma congenitale, osteosarcoma

INTRODUCTION

In 1868, Rothmund first described the association between skin lesions and cataracts. In 1923, Thomson reported the same cutaneous abnormalities associated with bone defects. Taylor joined these two syndromes together in 1957 and named it the *Rothmund-Thomson syndrome* (RTS), also known as *poikiloderma congenitale* [1]. This clinical entity is known to be associated with malignancies. We report three osteosarcoma cases in RTS patients.

CASE 1

M.B., born in 1972, experienced generalized eczema (initially localized on the face and then generalized) at 4 months with photosensitivity. By the age of 5, cutaneous lesions (atrophy, telangiectases, and pigmentation) were circumscribed to the face, limbs, and buttocks, associated with a healing defect. An x-ray checkup showed signs of former fractures, trabeculated metaphyses, widened long bone epiphyses, and iliac bone hypoplasia. Height and weight retardation, teeth abnormalities, thin eyebrows and hair, and puberty retardation with uterus hypoplasia were also present. These signs led to the diagnosis of Rothmund-Thomson syndrome. In 1988, M.B. presented a tumor on the upper left tibia extremity, revealed by nightly pain. A surgical biopsy confirmed an osteosarcoma. She received chemotherapy (Adriamycin and methotrexate) and a conservative surgery with replacement of the articulation with a prosthesis. Unfortunately, she presented infectious complications, leading to amputation, in 1989. In October 1993, M.B. was still alive with no evidence of disease.

CASE 2

F.V., born in 1976, presented with cutaneous lesions during the first month of life, compatible with constitutional eczema. A RTS diagnosis was assessed when he was 1 year old, because of poikiloderma lesions of the face, buttocks, and thighs with photosensitivity. Thin eyebrows, eyelashes, and hair, and height and weight retardation were also present. Bone x-rays showed the typical aspect: trabeculated bone and metaphyses defects. These x-rays also revealed a bifid third rib and several phalanx abnormalities. In 1982, the patient presented with a right femoral fracture with cortical effraction. The biopsy confirmed an osteosarcoma. He was treated by chemotherapy with methotrexate and local irradiation. The patient was in remission until January 1985, when he presented with a local and metastatic recurrence (nodes and lung) and died 5 months later.

CASE 3

S.T., born in 1977, was admitted in the hospital in 1987 because of a right ulna osteosarcoma. He was

From the Division of Pediatric Hematology-Oncology (I.C., F.M., J.-L.H.) and the Division of Pediatrics (J.-Y.C., A.D., H.A.-L.), University Hospital, Nantes, France.

Received May 24, 1995; accepted August 7, 1995.

Address reprint request to Dr. I. Cumin, Oncologie Pédiatrique, Centre Hospitalier Universitaire, Nantes 44000, France.

treated by surgery and chemotherapy with methotrexate. RTS was diagnosed because of irregular brownish pigmentation, a cutaneous red macula on the face and the hands, and typical skeletal abnormalities. No height retardation, but weight retardation was noted. The patient presented a soft tissue recurrence in May 1990, which was treated with amputation and second-line chemotherapy. The patient died in November 1991 with lung metastases.

DISCUSSION

The Rothmund-Thomson syndrome is an autosomal recessive hereditary disease with variable expression. It is more common in females (sex ratio = 4:3) [2]. Most cases occur with consanguinity, and the first cases were described in Switzerland and Bavarian Alps, where consanguinity is frequent [1,3,4]. None of our cases was linked to consanguinity. Skin lesions, skeletal defects, and cataract are constant in the RTS. Other possible abnormalities include growth retardation and teeth, nail and hair abnormalities. Other disorders appear to be probably random: glaucoma, myositis, myopathy, Raynaud syndrome, epilepsy, enteric malabsorption, and hypertension [2,5–8].

Skin lesions [9–13], essential for the diagnosis, occur in the first year of life in 90% of the cases, usually between 3 and 6 months of age. Initially, these lesions are red, limited, congestive, not itchy, localized on the face, and then spread to the ears, chin, forearms, and buttocks. By the age of 3–5 years, these lesions become atrophic, keratotic, and telangietatic. Verrucae are possible on the hands and feet. Photosensitivity is frequent but decreases with age [3]. Histologically, these lesions are totally nonspecific [14]. Electron microscopy shows only an accumulation of glycogen in the cytoplasm of keratinocytes. This suggests a dysregulation of skin metabolic activity [15]. More recent immunohistologic studies show Langherans cell abnormalities (in morphology and distribution), eventually related to cutaneous immunity defects [16]. Our three patients presented characteristic cutaneous lesions, and only two had sensitivity to sunlight.

Half of the patients with RTS present sparse hair, dystrophic nails, teeth abnormalities, and thin eyebrows and eyelashes. We have noted these abnormalities in two cases. Ocular anomalies occur in 50% of cases, usually cataracts, often bilateral, at between 3 and 7 years of age, which evolve rapidly. However, some published cases occurred as early as 4 months of age (before skin lesions) or very late, in the thirties or forties. Cornea lesions are also possible [3,17]. In sporadic cases no cataracts have been noted [18]. None of our cases presented with an ophthalmic abnormality.

Bone defects are present in more than half of the cases [3,19]. These abnormalities include: dysotosis, essentially involving the limbs; dysplasia, with trabeculated metaphyses; sclerosis and cystic abnormalities of the long bones; osteoporosis; and bone hypoplasia. Spontaneous fractures or fractures occurring after minor trauma are not uncommon and are often only seen on x-ray examinations. Skeletal changes increase with age [20]. All of these skeletal abnormalities contribute to the small stature present in half of the patients, and possibly noted before birth [5]. Two of our patients presented with a height retardation and bone defects related to the RTS.

Dental abnormalities are less common (20%): agenesia, microdontia, delayed and ectopic eruption, and supernumerary teeth. Dental abnormalities are also seen in "normal" members of the family, although they are not as frequent nor severe. It is suggested that these individuals are heterozygotes for RTS [4,21].

Hypogonadism in present in 25% of cases, with juvenile genital organs, amenorrhea, and sterility [9,22]. Other endocrine disturbances are unusual, such as parathyroid adenoma and disturbed thyroid function [23]. Intellectual development is retarded in 30% of cases [24]. No specific biological disorder is noted, although some authors reported isolated abnormalities: a decreased vitamin A blood level, a peak in the alpha-2-globulin fraction, and increased excretion of urinary glycosaminoglycans, probably related to a connective tissue disorder [3,25,26].

The association of RTS with malignancies has often been reported in the literature. This disease probably carries a genetic proclivity for developing malignancy at an early age. The most frequent malignancies reported are cutaneous epitheliomas (8% in Berg's publication) [9], such as basal cell or squamous cell epitheliomas, and Bowen's disease. These lesions usually appear in light-exposed areas. Their pathogenesis is unclear, and radiosensitivity, defective DNA repair such as in xeroderma pigmentosum, and a chromosomic defect have been suggested [2,27–29]. Some authors described skin epitheliomas only in keratotic lesions [5].

Other malignancies reported include gastric adenocarcinomas, fibrosarcomas, and osteosarcomas [2,25, 28,30–32]. Dick noted the occurrence of osteosarcomas at an earlier age, which was not confirmed by our series (onset at 6, 10, and 16 years old) [33]. Osteosarcomas seem to be the second most frequent malignancy in these patients. Osteosarcomas may occur with previous bone dysplasia. Consequently, x-rays must be interpreted very cautiously in RTS patients and should be repeated to detect skeletal defects. The treatment of these tumors does not differ from that for sporadic osteosarcoma, and the chemosensitivity and toxicity do not differ [34]. These patients need a very careful survey.

REFERENCES

1. Rook A, Whimster I: Congenital cutaneous dystrophy (Thomson's type). Br J Dermatol 61:197–205, 1949.

2. Sfar Z, Rihane E, Kamoun MR: Le syndrome de Rothmund-Thomson: à propos de quatre cas. Ann Pédiatr (Paris) 35:501–506, 1988.
3. Silver HK: Rothmund-Thomson syndrome: An oculocutaneus disorder. Am J Dis Child 111:182–190, 1966.
4. Ourgaud A, Payan H, Giraud F: Le syndrome de Rothmund: à propos d'une observation. J Genet Hum 24 (Suppl):151–164, 1976.
5. Nathanson M, Dandine M, Gaudelus J: Syndrome de Rothmund-Thomson avec glaucome: étude endocrinienne. Ann Pediatr 30: 520-525, 1983.
6. Dechenne C, Brumioul D, Chantraine JM: Un cas de maladie de Rothmund-Thomson avec hypertension. Ann Pediatr 29:665, 1982.
7. Lessem J, Bierre I, Forslund M: Epilepsy and myopathy in a patient with Rothmund-Thomson's syndrome. Acta Med Scand 207:237–239, 1980.
8. Srivastava RN, Azami S, Bhan MK: Rothmund-Thomson syndrome (poikiloderma congenital) in two sisters. Indian Pediatr 16:715–718, 1979.
9. Berg E, Chuang TY, Cripps D: Rothmund-Thomson syndrome: A case report, phototesting, and literature review. J Am Acad Dermatol 17:332-338, 1987.
10. Plantin P, Castel Y, Masse R: Poïkilodermie de Rothmund-Thomson: À propos du suivi sur vingt ans d'un cas déjà présenté dans la petite enfance. Ann Pédiatr (Paris) 34:635-638, 1987.
11. Taylor WB. Rothmund's syndrome-Thomson's syndrome. Arch Dermatol 75:236–244, 1957.
12. Vallet C, Prigent G, Jeanmougin M: Poïkilodermie congénitale (syndrome de Rothmund-Thomson). Ann Dermatol Venereol 110: 773–774, 1983.
13. Rodermund OE, Hausmann D: Das Thomson-syndrom: Ein Beitrag zu den kongenitalen Poikilodermien. Dermatol Monatsschr 163:601–612, 1977.
14. Castel Y. Masse R, Toudic L: Une observation de poïkilodermie congénitale (syndrome de Rothmund-Thomson) avec dystrophies majeures, nanisme très sévère et intolérance digestive. Ann Pediatr 24:647–651, 1977.
15. Shuttleworth D, Marks R: Epidermal dysplasia and skeletal deformity in congenital poikiloderma (Rothmund-Thomson syndrome). Br J Dermatol 117:377–384, 1987.
16. Sillevis-Smitt JH, Gons MH, Oorthuys JW: The poikiloderma of Rothmund-Thomson syndrome: Changes in Langherans cell morphology and distribution. Dermatologica 179:187–190, 1989.
17. Collins P, Barnes L, McCabe M: Poikiloderma congenital: Case report and review of the literature. Pediatr Dermatol 8:58–60, 1991.
18. Oates RK, Lewis MB, Walker-Smith JA: The Rothmund-Thomson syndrome: Case report of an unusual syndrome. Aust Paediatr J 7:103–107, 1991.
19. Febrer Bosch MI, Martinez Aparicio A, Clemente Garcia J: Poïkilodermie congénitale type Thomson avec dysplasies osseuses majeures. Ann Dermatol Venereol 111:429–433, 1984.
20. Kozlowski K, Scougall JS, Oates RK: Osteosarcoma in a boy with Rothmund-Thomson syndrome. Pediatr Radiol 10:42–45, 1980.
21. Kraus BS, Gottleib MA, Meliton HR: The dentition in Rothmund's syndrome. Am Dent Assoc 81:894–915, 1970.
22. Hall JG, Pagon RA, Wilson KM: Rothmund-Thomson syndrome wih severe dwarfism. Am J Dis Child 143:165–169, 1980.
23. Werder EA, Mürset G, Illig R: Hypogonadism and parathyroïd adenoma in congenital poikiloderma (Rothmund-Thomson syndrome). Clin Endocrinol 4:75–82, 1975.
24. Kassner EG, Qazi QH, Haller JO: Rothmund-Thomson syndrome (poikiloderma congenitale) associated with mental retardation, growth disturbance, and skeletal features. Skeletal Radiol 2:99–103, 1977.
25. Tokunaga M, Sato K, Funayama K: Rothmund Thomson syndrome associated with osteosarcoma. J Jpn Orthop Assoc 50:287–293, 1976.
26. Tokunaga M, Wakamatsu E, Yosizawa Z: Increased excretion of urinary glycosaminoglycans in a case of Rothmund-Thomson. Tohoku J Exp Med 126:1–6, 1978.
27. Lindlbauer R, Gschnait F, Zischinsky W: Syndrome de Rothmund-Thomson. Ann Dermatol Venereol 107:1045–1049, 1980.
28. Rebaud P, David L, Plauchu H: Observation familiale de syndrome de Rothmund-Thomson: Observation en faveur de l'unicité du syndrome. Association à un ostéosarcome. Pédiatrie 6:487–492, 1985.
29. Der-Kaloustian VM, McGill JJ, Vekemans M: Clonal lines of aneuploid cells in Rothmund-Thomson syndrome. Am J Med Genet 37:336–339, 1990.
30. Diem E: The Rothmund-Thomson syndrome. Hautarzt 26:425–429, 1975.
31. Davies MG: Rothmund-Thomson syndrome and malignant disease. Clin Exp Dermatol 7:455–457, 1982.
32. Starr DG, McClure JP, Connor JM: Non-dermatological complications and genetic aspects of the Rothmund-Thomson syndrome. Clin Genet 27:102–104, 1985.
33. Dick DC, Morley WN, Watson JT: Rothmund-Thomson syndrome and osteogenic sarcoma. Clin Exp Dermatol 7:119–123, 1982.
34. Varughese M, Leavey P, Smith P: Osteogenic sarcoma and Rothmund Thomson syndrome. J Cancer Res Clin Oncol 118:389–390, 1992.